REMARKS

Reconsideration of the present application is respectfully requested in view of the following remarks. Claims 43-50 are pending and under examination. Claims 49 and 50 are amended to correct the capitalization of the term "claim." No new matter has been added by the amendments.

REJECTIONS UNDER 35 U.S.C. § 103

A. Claims 43-45, 48, and 49 stand rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* (*Regional Anesthesia and Pain Medicine*, 18:4, 1993) and Grond *et al.* (*Pain* 79:15-20, 1999). Nickel *et al.* are alleged to teach that flupirtine is a centrally acting analgesic for treatment of pain, and that its use in combination with morphine increases the latter's analgesic activity, and also reduces morphine-induced tolerance, dependence, and behavioral changes. The Examiner agrees that Nickel *et al.* do not specifically teach treatment of neuropathic pain, but asserts that Nickel *et al.* confirm their observations in cancer patients, and then asserts that Grond *et al.* teach that neuropathic pain is one of the major problems of cancer pain treatment. The Examiner then asserts that it would have been obvious to use the combination of morphine and flupirtine for treating neuropathic pain, especially when associated with cancer.

B. Claim 46 stands rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* and Grond *et al.*, further in view of Perovic *et al.* (*Neurodegeneration* 4:369-374, 1995). Perovic *et al.* are alleged to teach that flupirtine is a clinically safe compound that is non-sedating in most cases, from which the Examiner alleges that it would have been obvious to use flupirtine in combination with negligible amounts of morphine to avoid overt sedation.

C. Claim 47 stands rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* and Grond *et al.*, further in view of Devulder *et al.* The Examiner relies on Nickel *et al.* and Grond *et al.* as above, and then alleges that Devulder *et al.* teach the recited dosages of flupirtine *alone* for treating neuropathic pain.

D. Claim 50 stands rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* and Grond *et al.*, further in view of Cleary (*Cancer Control*, 2000). Cleary is alleged to teach that cancer pain has a neuropathic component, and further identifies certain of the specific cancers in claim 50.

Applicants respectfully traverse the rejections in sections A-D above, and submit that the instant claims satisfy the requirements of non-obviousness over the cited references. Mainly, it is respectfully submitted that the Examiner has not established a *prima facie* case of obviousness for methods of using flupirtine and an opioid to treat neuropathic pain, specifically. *See In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of obviousness).

As acknowledged by the Examiner, Nickel *et al.* do not teach the treatment of neuropathic pain. Rather, they look at the effect of flupirtine's ability to inhibit nociceptive responses induced by chemical, thermal, mechanical and electrical stimuli. Without more, this reference provides no expectation that the combination of flupirtine and an opioid would have been effective at treating neuropathic pain, specifically, because it is well established that agents which target one type of pain do not necessarily work in other forms of pain. This is due to the diverse mechanisms and pathways which distinguish different pain types (*see, e.g.,* page 1, line 26 to page 4, line 21 of the instant specification for a description of the different mechanisms for the different types of pain).

Further, Nickel *et al.* are alleged to teach that flupirtine enhances the analgesic effects of opioids, particularly in cancer patients. Applicants respectfully disagree. In the Discussion section of Nickel *et al.*, it is stated that "*These findings indicate that flupirtine acts to produce antinociception through a central action in which opioid mechanisms play no role. Flupirtine causes antinociception via a mechanism involving a2-adrenoceptors, probably by activation or enhancement of descending noradrenergic inhibition. As such, one would expect this drug to be an effective non-opioid analgesic and to enhance the analgesic effects of opioids. Initial studies in cancer patients confirm these expectations.*" (emphasis added). Here, it is respectfully submitted that the authors merely hypothesize that the analgesic effects of the opioids might be enhanced, and no technical evidence are presented showing the effects in

patients. Absent such evidence, especially given the diverse mechanisms that distinguish the different types of pain, Applicants submit that mere hypothesizing is insufficient to establish a reasonable expectation for the specific purpose of treating neuropathic pain, a type of pain that this reference does not even consider.

The Examiner then combines Grond *et al.* with Nickel *et al.*, stating that Grond *et al.* teach employing an opioid analgesic and non-opioid analgesics for the treatment of neuropathic pain, and therefore alleges it would have been obvious to pick flupirtine as the non-opioid analgesic. Applicants respectfully disagree. There are thousands of non-opioid analgesics available, some of which are listed in Grond *et al.* The Examiner essentially alleges that from this list of thousands of non-opioid analgesics, it would have been obvious to select flupirtine and combine it with an opioid, despite the fact that of all of the non-opioids listed in *Grond et al.*, flupirtine was not even contemplated by that reference. Applicants respectfully submit that there is nothing in the teachings of Grond *et al.* that would lead the skilled artisan to combine flupirtine with an opioid in the treatment of neuropathic pain, specifically.

In view of these deficiencies, it is respectfully submitted that a *prima facie* case of obviousness has not been established for the treatment of neuropathic pain, as claimed.

Secondary Considerations of Non-Obviousness

Even assuming, *arguendo*, that a *prima facie* case of obviousness has been established, the patentability of the instant claims is strongly supported by secondary considerations of non-obviousness, which Applicants submit are sufficient to rebut any assumed *prima facie* case of obviousness.

Synergism as Evidence of Non-Obviousness. Applicants respectfully submit that the patentability of the instant claims is supported by secondary considerations of non-obviousness. Specifically, it is submitted that *synergism* may point toward non-obviousness. *See* M.P.E.P. § 2141(I). As detailed below, it is further submitted that the synergistic effects of the presently claimed subject matter are greater than expected from the art to an unobvious extent, and provide significant practical advantages in the treatment of neuropathic pain. *See*

M.P.E.P. § 716.02(a), citing *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991).

The combination of flupirtine and an opioid *synergistically* reduces symptoms of neuropathic pain (*see, e.g.,* page 45, lines 4-16 of the specification; and Figure 1 of the Declaration of Dr. Colin Stanley Goodchild, submitted herewith), thereby allowing the use of significantly reduced levels of opioids during neuropathic pain therapy, among other benefits. For example, Figure 1 of the Goodchild Declaration shows greater than additive anti-nociceptive effects for the combination of flupirtine and morphine, *i.e.,* an effect that is greater than the sum of the individual effects of flupirtine and morphine in that same experiment. Experiments also show that the same amount of analgesia can be achieved with a combination of flupirtine and morphine (*e.g.,* 4:1) as is obtained using the drugs individually, but with only *10% of the* ED_{50} *doses* of each drug in the fixed combination (*see, e.g.,* Figure 3 of the Goodchild Declaration). This phenomenon allows a *90% reduction* in the dose of each individual drug, and reveals a *highly* synergistic effect as the combination of flupirtine and an opioid is employed in the everyday treatment of neuropathic pain. The ability to achieve the same effects with a 90% reduction in the dosage of morphine represents a major advancement in the management of neuropathic pain, which, as far as Applicants are aware, can be found with no other combination of drug(s) and an opioid.

Applicants further submit that the synergistic properties of flupirtine in combination with an opioid are *unexpected*, whether in view of the cited art or other aspects of the art. For instance, even Nickel *et al.* at best suggest an *additive* increase in analgesic activity, and thus provide no technical basis to expect synergistic or greater than additive effects for the claimed combination of flupirtine and an opioid, especially those that allow a *90% reduction* in the dose of each individual drug. Also, other drugs have been used to increase the anti-nociceptive effects of opioids such as morphine, and none of these drugs have provided synergistic effects to that end. For instance, the use of gabapentin in combination with morphine as been known for some time (*see* also, Shimoyama *et al.*, *Pain* 72:375-382, 1997, abstract submitted herewith), and represents the current clinical "gold standard" for achieving anti-nociception without sedation in the treatment of neuropathic pain. However, gabapentin in

combination with morphine at best provides an additive effect, or less (*see* Figure 1 of the Goodchild Declaration). In contrast, as noted above, the direct comparative experiment of Figure 1 shows that flupirtine in combination with morphine *does* provide a substantially greater than additive effect. Other than wishful thinking, neither the cited art nor the state of the art provide any technical reason to expect the combination of flupirtine and morphine to provide *synergistic* effects in achieving anti-nociception without sedation in the treatment of neuropathic pain. Applicants therefore submit that superior results provided by the presently claimed combination are greater than those which would have been expected from the cited art to an unobvious extent.

The unexpected and superior properties of the instant claims also provide significant, practical advantages. As previously made of record, the synergistic results described herein, in which the claimed combination provides a result that is greater than the sum of the individual components (*i.e.,* a greater than additive result), demonstrate that flupirtine in combination with an opioid allows a therapeutically significant reduction (*e.g.,* 90% reduction) in the amount of either drug administered in order to obtain an analgesic effect, specifically for neuropathic pain. Among other benefits, these effects allow those undergoing neuropathic pain management therapy to reduce the risk of tolerance, avoid the life-interfering effects of overt sedation (*see, e.g.,* page 14, lines 23-29 of the instant specification), as well as manage other side effects, including euphoric effects, emetic effects, spastic constipation and increased smooth muscle tone (*see, e.g.,* page 4, lines 11-12 of the instant specification). As noted above, it is believed at present that these benefits can be found with no other combination of drug(s) and morphine. Accordingly, the synergistic effects of the claimed combination are not only greater than expected, but provide significant, real-world benefits in the treatment of neuropathic pain. Applicants therefore submit that the secondary considerations of non-obviousness clearly support the patentability of the instant claims.

In view of the remarks and evidence of record, Applicants submit that the instant claims satisfy the requirements of non-obviousness under 35 U.S.C. § 103(a), and respectfully request withdrawal of this rejection.

Applicants believe that all of the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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Enclosures:
§ 1.132 Declaration of Dr. Colin Stanley Goodchild
Shimoyama *et al. Pain* 72:375-382, 1997, abstract

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